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REMARKS

Claims 2-26 are pending, claims 2, 6-8, 10, 11, 13, and 14 having been amended and claims 15-26 having been added. The amendment to claims 6 and 7 is supported, *e.g.*, at page 7, lines 16-18. The amendment to claims 2, 8, 10, 11, and 13 are merely to clarify the scope and improve consistency among the claims, and do not alter their scope. Support for new claims 15-26 can be found, *e.g.*, at page 4, lines 1-5. No new matter has been added by this amendment. Claims 2-26 were rejected for obviousness under 35 U.S.C. § 103. Applicants request reconsideration and allowance of the claims.

The Examiner requested a list of co-pending or related applications. There are no co-pending or related U.S. applications. Related non-U.S. applications are:

Australian Application No. 54219/00

Canadian Application No. 2,375,874

European Application No. 99201788.9

European Application No. 00939007.1

Japanese Application No. 2001-501213

New Zealand Application No. 515685, issued as Pat. New Zealand Pat. No. 515685

Rejections Under 35 U.S.C. § 103

The Office Action alleges that the claimed invention is obvious over Arnold *et al.*, WO 98/41882 ("Arnold"). The Examiner states

> Multiple sclerosis, although not exemplified within Arnold's teaching to the extend ALS is discussed, is clearly encompassed in the teaching as one disease entity that is included among the 'neurologic diseases' to which [Arnold's diagnostic] procedure would be applicable. See page 3, lines 31-33. Riluzole administration is described as a treatment. See the Abstract. Accordingly, one skilled in the neurology art, in view of Arnold's teaching, would have been motivated to administer riluzole to treat multiple sclerosis, a disease characterized by neuronal damage and death, because the administration of riluzole results in an

increase in [N-acetylaspartate] levels. Arnold concludes an increase in NAA is indicative of a positive drug effect and suggests to the skilled artisan a treatment modality for multiple sclerosis.

This rejection is respectfully traversed. The claims are directed to methods for treating multiple sclerosis comprising administering to a patient a pharmaceutical composition comprising riluzole. Applicant disagrees that one would find in Arnold's disclosure a motivation to use riluzole to treat any particular condition other than ALS.

Arnold taught that NAA signal intensity, as measured by magnetic resonance spectroscopy (MRS), correlates with neuronal integrity and so can be used as a marker of neuronal integrity in the brain (Arnold, pages 1-2). Concerned with finding a non-invasive means to assess the efficacy of treatment of neurodegenerative diseases in general, Arnold proposed using NAA signal intensity as a surrogate marker for improvement in or loss of neuronal function during the course of any given treatment (page 3, lines 11-13). Arnold used riluzole treatment of ALS patients to demonstrate the principle, showing that NAA levels do rise with treatment with a drug already known to be efficacious in treatment of ALS. There is no suggestion that riluzole is some kind of all-purpose protector of neuronal integrity that would produce similar results in other types of neurodegenerative diseases. Different diseases can destroy neuronal and axonal function by very different mechanisms, requiring very different treatment modalities, yet all potentially giving the end result of loss of neuronal integrity (and concomitant loss of NAA signal). The fact that the same marker can be used for all of these very different conditions merely reflects the fact that the conditions all ultimately result in some type of neuronal or axonal damage. This can be readily illustrated by an example derived from Arnold itself. According to Arnold at page 2, lines 11-15, HIV infection can produce cognitive impairment that correlates with neuronal damage and thus a decrease in NAA level. Arnold goes on to suggest at page 6, lines 1-6, that zidovudine (*i.e.*, AZT) is one of several drugs that can be tested in accordance with Arnold's invention, utilizing NAA level as a surrogate marker of neuronal integrity. One of ordinary skill would understand that, while Arnold expects that zidovudine might produce an increase in NAA level in HIV-infected individuals, this would be a result of the antiviral effects of zidovudine, and not some general protective effect that applies to

the root causes of all neurodegenerative diseases. Even if Arnold had demonstrated that zidovudine actually increases NAA signal in HIV-infected individuals, no one would read that as a disclosure that this antiviral remedy should be used to treat ALS, MS, stroke, epilepsy, and Alzheimer's disease. The disclosure that a single surrogate marker (NAA level) permits one to monitor improvement in several neurodegenerative conditions does not amount to a teaching that a single drug will improve NAA level for all of the disclosed conditions. Yet this is exactly how the Examiner has interpreted the riluzole/ALS results in Arnold. Applicant submits that there is no motivation anywhere in Arnold to use riluzole to treat anything other than what it is known to be useful for (*i.e.*, ALS), just as there is no motivation to use zidovudine to treat anything other than what it is know to be useful for (retroviral infection).

Nor does Arnold provide the expectation of success that necessarily underpins any rejection for obviousness. Those skilled in the art know that success in treating neurological disorders is highly unpredictable. For example, numerous anti-glutamate agents have been tested for treatment of ALS, based on the hypothesis that glutamate excitotoxicity is a possible cause of the disease. None save riluzole proved to be effective against ALS in clinical trials. (See, *e.g.*, Testa *et al.*, *J. Neurol.*, 236:445-477, 1989; Askmark *et al.*, *J. of Neurol. Neurosurg. Psy.*, 56:197-200, 1993; Eisen *et al.*, *Can. J. Neurol. Sci.*, 20:297-301; abstracts attached as Exhibit A)

Furthermore, when riluzole was tested in a clinical trial for Parkinson's disease, based on its known properties as a glutamate antagonist, it was found to produce no meaningful effects on the symptoms of the disease (Jankovic and Hunter, *Parkinsonism Relat. Disord.*, 8:271-276, 2002; abstract attached as Exhibit B). It is clear that efficacy for this drug in one neurological disease (ALS) does not permit one to predict that the drug will be effective for another given neurological disease, even where there is a presumed etiological link between the two.

As the art provides neither motivation to use riluzole to treat MS, nor reasonable expectation of success upon doing so, Applicant requests withdrawal of the rejection under 35 U.S.C. § 103.

Enclosed is a Request for Continued Examination, an Information Disclosure Statement, a check for $90 for excess claim fees, a check for $770 for the Request for Continued Examination (RCE) fee, and a check for $950 for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: April 14, 2004

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Exhibit A

Branched-chain amino acids in the treatment of amyotrophic lateral sclerosis

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Summary. Thirty-two patients affected by amyotrophic lateral sclerosis (ALS) were included in a controlled, open therapeutic trial with branched chain amino acids (BCAA). Patients with bulbar muscle involvement were evaluated separately. No statistically significant differences were found in the clinical outcome between the patients treated and the control groups. Blood L-glutamate levels measured in eight patients were normal. The failure of BCAA in the treatment of the patients could be due to different disorders with unpredictable outcome included under the diagnosis of ALS.

Key words: Amyotrophic lateral sclerosis – Branched chain amino acids – Glutamate

Introduction

The aetiology and pathogenesis of amyotrophic lateral sclerosis (ALS) are still unknown and effective therapy has not yet been found [14].

The concentrations of amino acids have attracted interest, and abnormal amino acid levels in serum, cerebrospinal fluid and the nervous system have been occasionally reported [2, 5, 6, 11, 19]. Recently, attention has been drawn to a possible relationship between ALS and abnormal metabolism of glutamate [7–9]. Since L-leucine, L-isoleucine and L-valine (branched-chain amino acids, BCAA) could modify glutamate metabolism, they have been proposed as a useful form of treatment in ALS patients [10].

We report our preliminary experience in a trial of BCAA in 32 patients with ALS.

Patients and methods

Thirty-two consecutive patients with ALS were investigated in an open treatment study. The diagnosis was fully established by clinical and electromyographic criteria. The patients' clinical characteristics are shown in Table I.

The patients were divided in two main groups (16 bulbar and 16 non-bulbar patients), according to either the presence or absence of bulbar muscle involvement at the time of entry. Then, they were randomized to receive either BCAA or other drugs usually given in this disease. Thus four subgroups of 8 patients each were obtained.

Offprint requests to: D. Testa

Table 1. Patients' clinical characteristics

	Bulbar		Non-bulbar	
	BCAA	Control[a]	BCAA	Control
Male	6	4	7	5
Female	2	4[b]	1	3
Age (years) (range)	53.6 (49–60)	51.4 (49–61)	58.1 (40–60)	56.4 (45–71)
Illness duration[c] (range)	18.4 (4–36)	17.8 (13–32)	19.2 (5–48)	18.1 (4–36)

[a] Control groups consist of patients on therapy other than branched-chain amino acids (BCAA)
[b] patient with familial form
[c] Time interval in months between the time of examination and the time the patient thought he/she noticed the first symptom

BCAA powder consisting of 3 g L-leucine, 2 g L-isoleucine and 1.6 g L-valine was given orally four times daily. The patients were evaluated at entry and at 3-month intervals thereafter. Their clinical assessment was performed using the Norries scale [4]. The two main groups (bulbar and non-bulbar) were analysed separately.

Two criteria were used to evaluate the illness course: the number of patients dropping out of the trial because of either respiratory failure or need for nurse assistance, and rate of the score decline in each group. The number of patients in whom bulbar involvement appeared was also considered.

The significance was calculated by paired Student's *t*-test. In 8 out of 32 patients, the L-glutamate content was determined spectrophotometrically in deproteinized whole blood by measuring the conversion of nicotinamide-adenine dinucleotide (NAD) to the reduced form (NADH) [1]. We separated the patients with signs of bulbar palsy from the others because difficulty in swallowing could compromise the regular intake of BCAA powder.

Results

The four subgroups obtained (Table 1) were homogeneous with respect to mean age and illness duration. The proportion of males was slightly higher than that reported in the literature. In a 53-year-old female the disease occurred in the familial form; both her mother and a brother had died of ALS. The relationship between the familial and the sporadic forms of ALS has not been clearly established. It has been suggested

A pilot trial of dextromethorphan in amyotrophic lateral sclerosis

Håkan Askmark, Sten-Magnus Aquilonius, Per-Göran Gillberg, Lars Johan Liedholm, Erik Stålberg, Rolf Wuopio

Abstract

Assuming the presence of glutamate-induced neurotoxicity in amyotrophic lateral sclerosis 14 patients were treated with dextromethorphan, an N-methyl-D-aspartate receptor antagonist. The patients were treated with 150 mg dextromethorphan or placebo daily for 12 weeks in a double-blind crossover trial, with a wash out period of 4 weeks between the two treatment periods. Thereafter the surviving patients were treated with 300 mg dextromethorphan daily for up to 6 months in an open trial. No positive effects on clinical or neurophysiological parameters (relative number of axons, and compound muscle action potentials in the abductor digiti minimi muscle) were observed either in the double-blind trial or in the open trial.

(*J Neurol Neurosurg Psychiatry* 1993;56:197-200)

In recent years neuroexcitotoxic mechanisms have been suggested as possible causes both for sporadic amyotrophic lateral sclerosis (ALS)[1] and for the Guamanian form of ALS and Parkinson's dementia.[2] The hypothesis by Plaitakis[1] suggests that a generalised defect in excitatory amino acid metabolism in ALS may render a select group of neurons vulnerable to excitatory amino acid-induced neurotoxic damage because of their unique neuronal properties and the neurochemical character of their connections. Glutamate metabolism has been reported to be altered in ALS,[3-5] it has been suggested[6] that increased levels of synaptic glutamate could lead to pure excitation and degeneration of the motor neurons. Plaitakis *et al*,[1] who carried out a pilot trial of branched chain amino acids in ALS based on the theory that these amino acids might modify glutamate metabolism, have reported beneficial results from this treatment.

A subtype of glutamate receptor, the N-methyl-D-aspartate (NMDA) receptor, is thought to play a crucial role in glutamate-induced neuro-toxicity and it has been reported that specific antagonists to this receptor can exert protective effects against experimental neurodegeneration in which neuroexcitotoxic mechanisms have been implicated.[7]

In view of the hypothesis and findings mentioned above it seemed reasonable to examine whether dextromethorphan, an NMDA receptor antagonist,[8,9] has any beneficial effect in ALS.

Material and methods

Patients

Fourteen patients with ALS were included in the study, which was approved by the Ethics Committee of the Faculty of Medicine, University of Uppsala. The diagnosis was based on clinical findings and electro-myography according to the criteria developed by the World Federation of Neurology Subcommittee on Motor Neuron Disease.[10] All patients except two were ambulatory. Six patients had swallowing difficulties and four patients had respiratory symptoms. For patient data see table.

Three patients died during the study because of respiratory complications due to their ALS. Patient 2 died after four months of participation in the study, in her second week on dextromethorphan medication. Patient 12 died after 10 weeks of treatment with placebo

Table 1 Characteristics of patients treated

Patient Number	Sex	Age	Type	Duration (years)	Initial scores: Bulbar	Spinal	Norris	Muscle function tested*
1	M	50	mainly upper motor neuron involvement	2·5	7	98	42	A left, H right, H left
2	F	74	bulbar symptoms predominant	1·5	4	115	82	A left, E left, N right
3	F	47	mainly lower motor neuron involvement	5·0	15	118	92	H left, W right, W left
4	F	70	bulbar symptoms predominant	0·5	5	112	87	H right, H left, W left
5	M	61	mainly lower motor neuron involvement	1·5	15	119	93	H right, H left, W left
6	M	59	mainly lower motor neuron involvement	1·5	15	86	80	A right, H left, N
7	F	80	bulbar symptoms predominant	0·5	4	126	87	A right, E right, H left
8	M	58	mainly lower motor neuron involvement	3·0	15	62	60	E left, N left, W right
9	F	47	mainly lower motor neuron involvement	1·5	15	128	97	N, W right, W left
10	F	64	bulbar symptoms predominant	1·0	11	117	84	N, W right, W left
11	F	61	mainly lower motor neuron involvement	2·0	15	108	88	E left, H right, W left
12	F	73	bulbar symptoms predominant	1·0	10	127	89	E left, W right, W left
13	F	47	mainly lower motor neuron involvement	0·5	13	116	92	H right, E left, W left
14	M	69	mainly lower motor neuron involvement	1·0	15	114	73	A left, H right, N

Maximal values 15, 130, 100

*A = abduction of the arm; E = flexion of the elbow; H = flexion of the hip; N = flexion of the neck; W = extension of the wrist.

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Anti-Glutamate Therapy in Amyotrophic Lateral Sclerosis: A Trial Using Lamotrigine

Andrew Eisen, Heather Stewart, Michael Schulzer and Donald Cameron

ABSTRACT: Glutamate excitotoxicity is implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS). We report the results of a double blind, placebo controlled, trial using 100 mg of oral daily lamotrigine (3,5-diamino-6-(2,3 dichlorophenyl)-1,2,4-triazine) which inhibits glutamate release. 67 patients were entered and at trial termination of 1.5 years 15 had withdrawn (9 active and 6 placebo) and 12 had died (6 active and 6 placebo). Mean age at entry was 57.5 years for the active and 58.6 years for the placebo groups. Patients were seen at 3 monthly intervals and scored according to neurological deficit based upon age of onset, bulbar and respiratory involvement, ambulation and functional disability. The mean change in clinical scores for the active versus placebo groups over the trial period was 7.1 ± 3.3 and 9.0 ± 3.3 respectively ($0.05 < p < 0.10$). Changes in cortical threshold and MEP/CMAP ratios to magnetic stimulation also did not differ significantly between the two groups. We conclude that lamotrigine in the doses administered does not alter the course of ALS.

RÉSUMÉ: Thérapie anti-glutamate dans la sclérose latérale amyotrophique: un essai clinique avec la lamotrigine. L'excitotoxicité du glutamate est impliquée dans la pathogenèse de la sclérose latérale amyotrophique (SLA). Nous rapportons les résultats d'un essai thérapeutique à double insu, contrôlé par placebo, utilisant une dose quotidienne orale de 100 mg de lamotrigine (3,5-diamino-6-(2,3 dichlorophényl)-1,2,4-triazine) qui inhibe la libération du glutamate. 67 patients ont été admis dans l'étude; à la fin de l'étude, soit à 1.5 ans, 15 étaient sortis de l'étude (9 patients sous médication active et 6 sous placebo) et 12 étaient décédés (6 sous médication active et 6 sous placebo). L'âge moyen à l'entrée dans le protocole était de 57.5 ans pour le groupe sous médication active et de 58.6 ans pour le groupe sous placebo. Les patients étaient vus aux trois mois et le déficit neurologique était évalué sur la base de l'âge de début, de l'atteinte bulbaire et respiratoire, de la marche et de l'incapacité fonctionnelle. La moyenne du changement de la cote clinique entre le début et la fin de l'étude pour le groupe sous médication active était de 7.1 ± 3.3 alors qu'elle était de 9.0 ± 3.3 pour le groupe sous placebo ($0.05 < p < 0.10$). De plus, les changements du seuil cortical et du rapport MEP/CMAP à la stimulation magnétique n'étaient pas significativement différents entre les deux groupes. Nous concluons que la lamotrigine, à la dose utilisée au cours de cette étude, ne modifie pas l'évolution de la SLA.

Can. J. Neurol. Sci. 1993; 20: 297-301

The pathogenesis of amyotrophic lateral sclerosis (ALS) is unknown. However, amongst other potentially relevant factors, is the role of glutamate toxicity.[1-6] Glutamate is the principal fast excitatory neurotransmitter in the brain and can exert neurotoxic effects with induction of neuronal degeneration *in vivo* and *in vitro*.[6] Abnormalities of glutamate metabolism may also have a role in other neurodegenerative diseases.[1]

Lamotrigine [3,5-diamino-6(2,3 dichlorophenyl)-1,2,4-triazine] is a phenyltriazine compound originally synthesized as one of a sequence of folic acid antagonists which has been recently licensed for use in the U.K. and Ireland as an anticonvulsant in refractory epilepsy.[7] It acts mainly to inhibit excitatory amino-acid (glutamate) release and stabilizes neuronal membranes via blockade of voltage-sensitive sodium channels. It is completely absorbed after oral administration and a suggested maintenance dose for adults with epilepsy is 200 - 400 mg twice daily.[7]

The most common side effects reported include nausea, headache, diplopia, blurred vision, dizziness and ataxia. Skin eruptions occur in about 3% of patients. There have also been a few recorded deaths in epileptics on the drug who succumbed to a rapidly progressive illness with status epilepticus, disseminated intravascular coagulation and multiorgan failure. The relationship of these deaths to lamotrigine is uncertain.[7] Here we report the results of a randomized, double blind trial using lamotrigine in a dose of 100 mg daily in patients with ALS.

METHODS

Study Design

We used a double blind placebo controlled trial. The study was designed as a survival trial with death as the end point. In addition clinical and electrophysiological data were analyzed.

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☐ 1: Parkinsonism Relat Disord. 2002 Mar;8(4):271-6.

ELSEVIER FULL-TEXT ARTICLE

A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease.

Jankovic J, Hunter C.

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BACKGROUND: To the extent that excitotoxicity may play a role in the pathogenesis of certain neurodegenerative disorders, antagonists of glutamate, an excitatory neurotransmitter, should exert neuroprotective effects in these disorders, including Parkinson's disease (PD). METHODS: Patients in early stages of PD, not previously treated with levodopa, were randomized to receive riluzole 50mg capsules orally, taken twice daily or a matching placebo. All subjects were evaluated at baseline (pre-treatment), at 1, 3 and 6 months (post-treatment), and following a 6-week washout. After the washout, all subjects were offered an enrollment in an open label, 1-year, extension study. The principal investigator (JJ), however, remained blinded to the original assignment during the entire study. The patients were assessed by the Unified Parkinson's Disease Rating Scale (UPDRS), Activities of Daily Living (ADL), Hoehn & Yahr (HY) stage, and Schwab and England (SE) ADL scale. The quantitative assessments included Movement Time (MT) and Reaction Time (RT). Additionally, the time to initiate dopaminergic therapy was assessed. Safety was determined at each visit by clinical history and examination, a panel of blood safety laboratory tests including complete blood count, chemistry profile, and liver function studies. RESULTS: Twenty patients with a mean age of 62+/-9.02 (range: 46-73) years and mean duration of symptoms of 18+/-9.53 (range: 6-36) months were enrolled. One patient withdrew from the study because he needed more aggressive treatment of his symptoms. Analysis of the efficacy variables showed no meaningful symptomatic effect of riluzole on UPDRS score. Likewise, there was no significant change in the median HY stage, SE ADL rating, or the MT/RT. Seventeen patients (mean age 62+/-9.26) elected to continue in the open label extension study. Although the observed deterioration in UPDRS scores seemed to be more pronounced in the placebo group than in the riluzole group, the difference did not reach statistical significance. There was no statistically significant difference in the latency between enrollment and start of symptomatic therapy when patients initially treated with riluzole were compared to those initially treated with placebo (8.3 vs 9 months). CONCLUSIONS: This pilot and extension study showed that riluzole, 100mg/day, was well tolerated in patients with early PD. No evidence of symptomatic effect of riluzole was observed. Because of the exploratory nature of the design and small size of the study, it was not possible to determine whether riluzole affected the natural history of PD. The encouraging results from our study, however, suggest that larger, longitudinal studies are warranted.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

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